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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,002	05/30/2001	Brett P. Monia	ISPH-0578	9404

26259 7590 11/26/2002

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	10

DATE MAILED: 11/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,002	MONIA ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 12-20 and Species of H-Ras and Gemcitabine in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions are not distinct and no burden exists. This is not found persuasive because the groups, product and methods, represent one of the classic situations which MPEP 806.06(h) identifies as distinct if the product can be used for different purposes. The restriction clearly sets forth alternate uses for the product such as measurement of polymerase sensitivity and therefore the invention is properly distinct. With regard to the issue of burden, the separate classification of the two groups is prima facie evidence of burden which applicant has not rebutted.

The requirement is still deemed proper and is therefore made FINAL.

Priority

2. Applicant claims priority to a series of applications beginning with 09/575,554, the immediate parent. In a review of the 09/575,554 specification the examiner found absolutely no support for the combination of the antisense therapy with another therapy and in particular, no support for a method of modulating expression using an antisense combined with a chemotherapeutic agent such as gemcitabine. In the absence of such support, the claims receive an effective filing date of the current specification or May 30, 2001. Applicant is welcome to identify such support in the parent application by page and line number.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 12-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Calabretta et al (WO 94/08625).

This 102 rejection is made against the genus claim with regard to the chemotherapeutic agent and with regard to ras.

Calabretta teaches a method for modulating the expression of human ras, including N-ras, H-ras and K-ras (see page 16, lines 1-9, page 85-86, claims 16 and 17) comprising:

(a) contacting tissue or cells containing a human ras gene (see page 13, lines 19-37 and page16, lines 1-9) with an effective amount of a composition comprising an oligonucleotide which is targeted to a nucleic acid encoding human ras and which is capable of inhibiting ras expression (see page 13, lines 19-37, page 16, lines 1-9 and page 17, line 4 to page 22, line 2, page 85-86, claims 16 and 17) and at least one chemotherapeutic agent such as doxorubicin (see page 22, line 14 to page 23, line 25, page 85-86, claims 16 and 17),

whereby expression of ras is modulated (see page 16, lines 1-9, page 85-86, claims 16 and 17).

Calabretta teaches the use of an amount which kills cancer cells while sparing normal hematopoietic (blood) cells (see page 14, lines 8-17).

Calabretta expressly teaches that the method can be used to treat diseases (see page 31, lines 10-24) including ras associated diseases such as the hyperproliferative condition of colon cancer (see page 32, lines 14-17).

Calabretta teaches purging of bone marrow (see page 38, lines 12-31) which inherently comprises some peripheral blood mononuclear cells.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The 103 rejection is made against the elected species.

7. Claims 12-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Calabretta et al (WO 94/08625) in view of Possinger et al (Anti-cancer Drugs (1995) 6:suppl 6 pp. 55-59).

Calabretta teaches a method for modulating the expression of human ras, including N-ras, H-ras and K-ras (see page 16, lines 1-9, page 85-86, claims 16 and 17) comprising:

(a) contacting tissue or cells containing a human ras gene (see page 13, lines 19-37 and page16, lines 1-9) with an effective amount of a composition comprising an oligonucleotide which is targeted to a nucleic acid encoding human ras and which is capable of inhibiting ras expression (see page 13, lines 19-37, page 16, lines 1-9 and page 17, line 4 to page 22, line 2, page 85-86, claims 16 and 17) and at least one chemotherapeutic agent (see page 22, line 14 to page 23, line 25, page 85-86, claims 16 and 17),

whereby expression of ras is modulated (see page 16, lines 1-9, page 85-86, claims 16 and 17).

Calabretta teaches the use of an amount which kills cancer cells while sparing normal hematopoietic (blood) cells (see page 14, lines 8-17).

Calabretta expressly teaches that the method can be used to treat diseases (see page 31, lines 10-24) including ras associated diseases such as the hyperproliferative condition of colon cancer (see page 32, lines 14-17).

Calabretta teaches purging of bone marrow (see page 38, lines 12-31) which inherently comprises some peripheral blood mononuclear cells.

While Calabretta expressly suggests combination therapy using the antisense oligonucleotides with chemotherapeutic agents including antimetabolites (See page 22, lines 1-22), Calabretta does not teach combination of the antisense with the antimetabolite Gemcitabine for cancer treatment.

Possinger teaches the use of Gemcitabine for treatment of cancer (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Calabretta to use Gemcitabine in the combination therapy since Calabretta expressly teaches "The non-antisense component of the therapeutic combination may comprise an antineoplastic (anti cancer) agent useful in the treatment of the particular disease state characterized by the expression of the targeted oncogene/proto-oncogene (see page 22, lines 5-9)". Calabretta further notes that H-ras is associated with breast cancer (see page 32, line 16). Motivation to use Gemcitabine in combination with the antisense is derived from Possinger who states "Gemcitabine's modest toxicity profile and single-agent activity make it an attractive candidate for trial in combination therapy in advanced breast cancer (abstract)". Possinger also notes that "Gemcitabine is a logical candidate for combination chemotherapy (see page 59, column 1)". An ordinary practitioner would have been motivated to use the antimetabolite Gemcitabine in the place of other antimetabolites expressly recited by Calabretta in his combination therapy for treatment of H-ras based cancers since Gemcitabine is expressly suggested by Possinger for use in combination therapies such as those of Calabretta and since Gemcitabine has low toxicity and good activity against cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

November 26, 2002